PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 September 2000 (01.09.00)	
International application No. PCT/NZ99/00198	**Applicant's or agent's file reference** 25268 SMR
International filing date (day/month/year) 26 November 1999 (26.11.99)	**Priority date** (day/month/year) 26 November 1998 (26.11.98)
Applicant VICKERS, Mark, Hedley et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 June 2000 (21.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Manu Berrod
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US) PCT/NZ99/00198

PATENT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

MONK, Jonathan, Paul
Baldwin Shelston Waters
NCR Building
342 Lambton Quay
Wellington 6001
NOUVELLE-ZÉLANDE

Date of mailing (day/month/year)
08 January 2001 (08.01.01)

Applicant's or agent's file reference
JM503272/142

IMPORTANT NOTIFICATION

International application No.
PCT/NZ99/00198

International filing date (day/month/year)
26 November 1999 (26.11.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
BENNETT, Michael, Roy
West-Walker Bennett
Mobil on the Park
157 Lambton Quay
Wellington
New Zealand

State of Nationality

State of Residence

Telephone No.
+64 4 499 9058

Facsimile No.
+64 4 499 9306

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
MONK, Jonathan, Paul
Baldwin Shelston Waters
NCR Building
342 Lambton Quay
Wellington 6001
New Zealand

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
J. Leitao

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 003757851

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 25268 SMR	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/NZ 99/00198**	International filing date *(day/month/year)* 26 November 1999	Priority Date *(day/month/year)* 26 November 1998
International Patent Classification (IPC) or national classification and IPC **Int. Cl.**[7] A61K 38/27; A61P 9/12		
Applicant 1. AUCKLAND UNISERVICES LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **3** sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of **7** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand 21 June 2000	Date of completion of the report 09 March 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer A. WILCOX Telephone No. (02) 6283 2243

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ 99/00198

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1, 5-11,** as originally filed,
pages , filed with the demand,
pages **2, 3, 4, 4a,** received on **05 February 2001** with the letter of **05 February 2001.**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **12, 13 and 14,** received on **05 February 2001** with the letter of **05 February 2001.**

☒ the drawings, pages **1/2 - 2/2,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:
☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/fig

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 19	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1 - 19	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1 - 19	YES
	Claims	NONE	NO

2. Citations and explanations (Rule 70.7)

Citations

(a) AU 21490/97 (Pharmacia & Upjohn AB) 12 April 1996,
(b) Saloman, F. et al, The Effects of Treatment with Recombinant Human Growth Hormone On Body Composition and Metabolism In Adults With Growth Hormone Deficiency. The New Zealand Journal of Medicine. 1989, 321 : 1997-1803,
(c) Rosen, Thord et al, Cardiovascular Risk Factors In Adult Patients With Growth Hormones Deficiency. Acta Endocrinologica, 1993, 129 : 195-200,
(d) Jorgenson, Jens O.L. et al, Adult Growth Hormone Deficiency. Hormone Research. 1994; 45 : 235-241.

Explanations

The claims (filed 5 February 2001) are considered to be novel and to have an inventive step when compared with the publications cited in the International Search Report. The claims are limited by the feature of treating hypertension in a mammal which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment and that feature is not described in the publications cited in the International Search Report. The publications cited in the International Search Report describe the use of Growth hormone to treat Adult Growth Hormone Deficency and Metabolic Syndrome.

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 38/27, A61P 9/12

A3

(11) International Publication Number: WO 00/30588

(43) International Publication Date: 2 June 2000 (02.06.00)

(21) International Application Number: PCT/NZ99/00198

(22) International Filing Date: 26 November 1999 (26.11.99)

(30) Priority Data:
333035 26 November 1998 (26.11.98) NZ

(71) Applicant *(for all designated States except US)*: AUCKLAND UNISERVICES LIMITED [NZ/NZ]; UniServices House, 58 Symonds Street, Auckland (NZ).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: VICKERS, Mark, Hedley [GB/NZ]; 1 Nordon Place, Remeura, Auckland (NZ). BREIER, Bernhard, Hermann, Heinrich [DE/NZ]; 1 Edenvale Crescent, Mt Eden, Auckland (NZ). IKENASIO, Bettina, Anastasia [NZ/NZ]; 2–B Emerson Street, Glendowie, Auckland (NZ).

(74) Agents: BENNETT, Michael, Roy et al.; West–Walker Bennett, Mobil on the Park, 157 Lambton Quay, Wellington (NZ).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
5 October 2000 (05.10.00)

(54) Titl : TREATMENT OF HYPERTENSION

(57) Abstract

The invention provides a method of treating hypertension, particularly in individuals that have experienced intrauterine fetal programming or an adverse post–natal environment. The method comprises administering an agent which is a ligand that binds to and activates the growth hormone receptor. Preferably, growth hormone, an analog thereof or a functionally equivalent ligand is administered.

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
25268 SMR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NZ99/00198	26 November 1999	26 November 1998
Applicant: AUCKLAND UNISERVICES LIMITED et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure N .

[ ] as suggested by the applicant.

[X] None of the figures

[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ99/00198

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 38/27; A61P 9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 24190/97 (Pharmacia & Upjohn AB) 12 April 1996 A61K 38/27 23 October 1997 Claims 1, 11, page 11, lines 10-14	1, 2, 5-8, 10, 13, 15-17 20-22 and 24-27. 9, 14
X	Salomon, Franco, Cuneo, Ross, C. Hesp, Richard and Sönksen, Peter, H. The Effects of Treatment with Recombinant Human Growth Hormone On Body Composition and Metabolism In Adults With Growth Hormone Deficiency. The New Zealand Journal of Medicine 1989; 321:1797-1803.	1, 2, 5-8, 10, 13, 15-17, 20, 22 and 24-27

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2000	09 JUNE 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **A Wilcox** Telephone No : (02) 6283 2243

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ99/00198

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Rosen, Thord, Eden, s., Larson, G., Willhelmsen, Lars and Bengtsson, Bengt-Ake. CARDIOVASCULAR RISK FACTORS IN ADULT PATIENTS WITH GROWTH HORMONE DEFICIENCY. Acta Endocrinologica. 1993; 129:195-200.	1, 2, 5-8, 10, 13, 15-17, 20-22 and 24-27.
X	Jorgensen, Jens O.L. et al. ADULT GROWTH HORMONE DEFICIENCY. Hormone Research. 1994; 42:235-241.	1, 2, 5-8, 10, 13, 15-17, 20-22 and 24-27

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ99/00198

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	24190/97	WO	9738709	EP	935469	CA	2250907

END OF ANNEX

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K | A2

(11) International Publicati n Number: **WO 00/30588**

(43) International Publication Date: 2 June 2000 (02.06.00)

(21) International Application Number: PCT/NZ99/00198

(22) International Filing Date: 26 November 1999 (26.11.99)

(30) Priority Data:
333035 26 November 1998 (26.11.98) NZ

(71) Applicant *(for all designated States except US)*: AUCKLAND UNISERVICES LIMITED [NZ/NZ]; UniServices House, 58 Symonds Street, Auckland (NZ).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: VICKERS, Mark, Hedley [GB/NZ]; 1 Nordon Place, Remeura, Auckland (NZ). BREIER, Bernhard, Hermann, Heinrich [DE/NZ]; 1 Edenvale Crescent, Mt Eden, Auckland (NZ). IKENASIO, Bettina, Anastasia [NZ/NZ]; 2–B Emerson Street, Glendowie, Auckland (NZ).

(74) Agents: BENNETT, Michael, Roy et al.; West–Walker Bennett, Mobil on the Park, 157 Lambton Quay, Wellington (NZ).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: TREATMENT OF HYPERTENSION

(57) Abstract

The invention provides a method of treating hypertension, particularly in individuals that have experienced intrauterine fetal programming or an adverse post–natal environment. The method comprises administering an agent which is a ligand that binds to and activates the growth hormone receptor. Preferably, growth hormone, an analog thereof or a functionally equivalent ligand is administered.

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TREATMENT OF HYPERTENSION

FIELD OF THE INVENTION

This invention relates to the treatment of hypertension, and more particularly to the treatment of hypertension in individuals following intrauterine programming of cardiovascular pathophysiology.

BACKGROUND

It is known that disordered fetal growth which is caused by many events including maternal undernutrition during pregnancy, as well as having immediate effects on the fetus, may have long term health consequences for individuals (Barker, D.J. Outcome of low birthweight, *Hormone Research* 42:223-230, 1994; Barker, D.J. Growth in utero and coronary heart disease, *Nutr Rev.*, 52:S1-S7, 1996). In particular, it has become evident that in addition to the well recognised long term sequelae of persistent growth failure, disordered fetal growth is associated with a higher incidence of hypertension, cardiovascular, cerebrovascular and metabolic disorders in adulthood. (Barker, D.J. Outcome of low birthweight, *Hormone Research* 42:223-230, 1994; Barker, D.J. Growth in utero and coronary heart disease, *Nutr Rev.*, 52:S1-S7, 1996; Woodall, S.M., *et al.*, Chronic Maternal Undernutrition in the Rat Leads to Delayed Postnatal Growth and Elevated Blood Pressure in Offspring, *Pediatr. Res.* 40: 438-443, 1996).

Hypertension, or high blood pressure, is a particularly significant problem in the adult population. This is because it is common, its consequences are far reaching and can be devastating and the symptoms do not show until late in its course. High blood pressure is one of the major risk factors for coronary heart disease and strokes. It can also lead to congestive heart failure, aortic dissection, and renal failure. Over half of patients with angina pectoris, sudden death, stroke, and atherothrombotic occlusion of the abdominal aorta or its branches have hypertension. Greater than 70% of people with dissecting aortic aneurysm, intracerebral haemorrhage, or rupture of the myocardial wall have high blood

pressure. It is a major risk factor for atherosclerosis. Treatment of high blood pressure can prolong life. Screening programmes reveal that 25% of the general population are hypertensive (Schoen, F.J. (1994). Blood Vessels. In Robbins Pathologic Basis of Disease. Edited by R.S. Cotran, V. Kumar, and F.J. Schoen. Philadelphia: W.B. Saunders Company. 467-516). The prevalence of high blood pressure increases with age. However, in older age groups the disease is usually relatively mild compared to that in young adults where it is often more severe. Approximately 90 to 95% of hypertension is idiopathic and of the remaining 5 to 10%, most is secondary to renal disease. Both primary and secondary hypertension may be either benign or malignant.

In the majority of cases, hypertension remains at a modest level and fairly stable from years to decades. However, if the raised blood pressure is not controlled by anti-hypertensive agents, it frequently causes disability and death from heart failure, and substantially increases the risk of myocardial infarction and strokes. Approximately 5% of people have malignant hypertension where blood pressure rapidly increases and if left untreated, leads to death in one to two years.

Recognising the significance of the problem, it is an object of the present invention to provide a method of treating hypertension, in at least a subset of the population (individuals which experienced intrauterine undernutrition or growth retardation or an adverse postnatal environment), or at least to offer the public a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect the present invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an

agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

In another aspect, the present invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of growth hormone, an analog thereof, or a functionally equivalent ligand.

Generally, the hypertensive state of the mammal will be the result of intrauterine fetal programming, or of an unfavorable/adverse postnatal environment (eg. a hypercaloric diet). However, any mammal with hypertension can be treated in accordance with the above methods.

Preferably, the mammal to be treated is an adult mammal.

As used herein, the term "intrauterine undernutrition or growth retardation" means disordered fetal growth with causes which include maternal undernutrition, placental insufficiency, endocrine abnormalities and substance abuse, as evidenced by a relatively low birth weight.

As used herein, "analog" means a protein which is a variant of growth hormone through insertion, deletion or substitution of one or more amino acids but which retains at least substantial functional equivalency.

The term "functionally equivalent ligand" means an agent which binds to and activates the receptors which growth hormone binds to and activates to give the anti-hypertensive effect.

In a further aspect, the invention provides a method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

The method is particularly suitable for treating a mammal which has experienced either an adverse fetal environment, an adverse postnatal environment, or both.

Preferably, the effective concentration of said growth hormone analog or ligand is increased through direct administration.

Preferably, the effective concentration of growth hormone is increased through direct administration of growth hormone.

Alternatively, the effective concentration of growth hormone is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Preferably, the mammal is an adult human.

In a further aspect, the present invention provides the use of an agent selected from growth hormone, an analog thereof or a functionally equivalent ligand in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment.

In yet a further aspect, the invention provides the use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal

environment, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Although the invention is broadly as defined above, it also includes embodiments of which the following description provides examples.

BRIEF DESCRIPTION OF THE DRAWINGS

In particular, the invention will be better understood with reference to the accompanying drawings, in which:

Figure 1 shows the mean systolic blood pressure in *ad-libitum* and developmentally programmed (DP) rat offspring. The data is mean ±SEM with a minimum of 5 animals per group; and

Figure 2 shows the percent change in systolic blood pressure in the rats following rbGH treatment for 21 days. The data is mean ±SEM, minimum of 5 animals per group.

DESCRIPTION OF THE INVENTION

The focus of the invention is on the treatment of hypertension. It is particularly on the treatment of hypertension in a subset of the adult population. The applicant's surprising finding, which underlies the present invention, is that administration of growth hormone to an adult mammal with hypertension can reduce systolic blood pressure. This is particularly true for mammals which have been subject as a fetus to adverse cardiovascular programming during pregnancy or which have undergone intrauterine growth retardation (IUGR), and have therefore been "programmed" to subsequently develop hypertension.

This finding with respect to growth hormone is unexpected given the previous reports associating an increase in systolic blood pressure with long-term exposure to endogenous growth hormone in acromegalics (Sacca, L., *et al.*, Growth Hormone and the Heart. Endocrine Reviews, Vol 15, No. 5, 555-573 [1994]) and low systolic blood pressure after a long-term lack of exposure to endogenous growth hormone in growth hormone deficient adults (Sacca, L., *et al.*, Growth Hormone and the Heart. Endocrine Reviews, Vol 15, No. 5, 555-573 [1994]). In other studies, growth hormone has been reported to decrease diastolic blood pressure (Johannsson, G., *et al.*, Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism and reduces diastolic blood pressure. *Journal of Clinical Endocrinology and Metabolism*, Vol 82, No. 3 727-734 (1997)), while having no effect on systolic pressure.

The invention therefore provides a method of treating hypertension in a mammal, such as a mammal which has experienced intrauterine growth retardation or under-nutrition or which has experienced a long term adverse postnatal environment such as hypocaloric or hypercaloric nutrition. It is however envisaged that the invention will have application in treating mammalian hypertension caused by other aetiologies, risk factors and environmental effects.

It is also envisaged that the principal application of the method of the invention will be to adult humans although treatment of pre-adult and non-human mammals is in no way excluded.

In a preferred aspect, the method of the present invention involves administering to the mammal an effective amount of growth hormone, an analog thereof or a functionally equivalent ligand. In a preferred embodiment, growth hormone itself is administered to the mammal.

The growth hormone can be any mammalian growth hormone, with examples being human growth hormone, bovine growth hormone, rat growth hormone and porcine growth hormone. It is however preferred that the growth hormone employed be human growth hormone where the mammal is a human.

The growth hormone which is used in this invention can be obtained from any commercial source.

In addition to growth hormone itself, the use of analogs of growth hormone or functionally equivalent ligands of growth hormone is contemplated.

A protein is a functional equivalent of another protein for a specific function if the equivalent protein is immunologically cross-reactive with, and has at least substantially the same function as, the original protein. The equivalent can be, for example, a fragment of the protein, a fusion of the protein with another protein or carrier, or a fusion of a fragment with additional amino acids. For example, it is possible to substitute amino acids in a sequence with equivalent amino acids using conventional techniques. Groups of amino acids normally held to be equivalent are:

(a) Ala, Ser, Thr, Pro, Gly;
(b) Asn, Asp, Glu, Gln;
[c] His, Arg, Lys;
(d) Met, Leu, Ile, Val; and
(e) Phe, Tyr, Trp.

It will also be appreciated that the present invention also extends to the administration of an agent which either stimulates production of growth hormone, or which lessens or prevents inhibition of growth hormone activity, ie to the administration of growth hormone agonists or secretagogues (substances which effect a direct increase in production of growth hormone).

Examples of agents which stimulate growth hormone and production or lessen or prevent its inhibition include growth hormone releasing peptides (GHRP) such as GHRP-1, GHRP-2, GHRP-6, hexarelin, G-7039, G-7502, L-692,429, L-692,585, L-163,191 or growth hormone releasing hormone (GHRH) or inhibitors of growth hormone antagonists (substances which bind growth hormone or otherwise prevent or reduce the action of growth homone within the body). These latter compounds exert an indirect effect on effective growth hormone concentrations through the removal of an inhibitory mechanism, and include substances such as somatostatin release inhibitory factor (SRIF).

The active agent can be administered using any suitable route. Where growth hormone is the active compound to be administered, it will generally be administered as an injectable formulation, in combination with one or more suitable carriers or excipients. Those persons skilled in the art will appreciate how suitable formulations can be prepared.

The active agent can also be administered in combination. For example, a combination of growth hormone and other conventional anti-hypertensive agent(s), for example ACE (angiotensin-converting enzyme) inhibitors such as quinapril, is also contemplated.

Another possibility is administration of a replicable vehicle encoding the growth hormone/analog/ligand to the patient. Such a vehicle (which may be a modified cell line or virus which expresses growth hormone/analog/ligand within the patient) could have application in increasing the concentration of the active compound within the patient for a prolonged period. Such a vehicle could well form part of an implant.

Dosage levels will be formulation dependent. However, by way of example, the recommended dosage rate of growth hormone formulated for injection would be in the range of 0.1ug/kg/day to 1mg/kg/day. A preferred dosage rate would be from approximately 2 to 200 ug/kg/day.

The invention will now be further described with reference to the following non-limiting examples.

EXAMPLES

Experimental

Virgin Wistar rats (age 100±5 days, n=15 per group) were time mated using a rat oestrous cycle monitor (Fine Science Tools INC., North Vancouver, BC, Canada) to assess the stage of oestrous of the animals prior to introducing the male. Day 1 of pregnancy was determined by the presence of spermatozoa after a vaginal smear. After confirmation of mating, rats were housed individually in standard rat cages containing wood shavings as bedding and with free access to water. All rats were kept in the same room with a constant temperature maintained at 25°C and a 12-h light:12-h darkness cycle. Dams were randomly assigned to receive food either *ad-libitum* (n=30, 15 study animals and 15 dams for crossfostering) or to receive 30% of *ad-libitum* (determined by measuring food intake on the previous day of an *ad-libitum* fed dam). The diet composition was protein 18%, fat 4%, fibre 3%, ash 7% and carbohydrate 58% (Diet 86, Skellerup Stock Foods, Auckland, New Zealand). Food intake and body weights were recorded daily.

Following birth, offspring from restricted fed dams were crossfostered onto *ad-libitum* fed mothers. Crossfostering is necessary due to lactational insufficiency in restricted fed dams. Litter size was adjusted to 8 pups per litter. Pre-weaning weights of all pups were recorded daily. At weaning (age 21 days) pups were sexed and housed in cages (males 2 per cage, females 3 per cage) and fed one of three diets regimes (normal, *hyper*caloric and *hypo*caloric (70% of normal)) *ad libitum* for the remainder of the study. At 90±5d (corresponding to adulthood), systolic blood pressure recordings were taken (n=12 per group).

Treatment was then commenced for 21 days with recombinant bovine growth hormone (rbGH) at a dose of 10ug/g/day given over 2 subcutaneous injections (8am and 5pm). Control animals were treated with carbonate buffered saline (CBS, pH 9.4) using an identical protocol. Immediately prior to sacrifice (24-48hrs), a repeated systolic blood pressure recording was taken using identical conditions (method is outlined below).

Normal and Hypercaloric Diets

Two custom made diets were prepared for the study. The composition of the diets was as follows:

Control diet:	protein 19.4%, fat 5%, fibre 5%, salt 1.5%, 2959 kcal/kg
Hypercaloric diet:	protein 30%, fat 30%, fibre 5%, salt 1.5%, 4846 kcal/kg

Both diets had a protein/energy ratio of 26%. Hypocalorically fed animals were given 70% of the intake of the DP control fed animals.

Methods

Systolic blood pressures were recorded by tail cuff plethysmography according to the manufacturer's instructions (Blood pressure analyser IITC, Life Science, Woodland Hills, CA, USA). Rats were restrained in a clear plastic tube in a heated room (25-28 °C). After the rats had acclimatised (10-15min) the cuff was placed on the tail and inflated to 240mmHg. Pulses were recorded during deflation at a rate of 3mmHg/sec and reappearance of a pulse was used to determine systolic blood pressure. A minimum of 3 clear systolic blood pressure recordings were taken per animal. Coefficient of variation for repeated measurements was <5%.

Results

Prior to onset of growth hormone therapy, developmentally programmed (DP) offspring showed a marked degree of hypertension as compared to *ad-libitum* offspring on a control diet ($p < 0.001$). Systolic blood pressure in DP offspring was further exacerbated by exposure to *either* a hypercaloric or hypocaloric diet postnatally ($p<0.001$, Figure 1).

Systolic blood pressure was significantly decreased in all DP animals treated with rbGH for 21 days (Figure 2). Although *ad-libitum* animals on a hypercaloric diet showed a significant increase in systolic blood pressure prior to treatment, growth hormone therapy did not reduce the degree of hypertension observed in these animals. Similarly, offspring from *ad-libitum* control fed mothers showed no significant change in systolic blood pressure following treatment. The reduction in systolic blood pressure was most marked in the DP animals fed hypocalorically. *Ad-libitum* and DP offspring treated with vehicle only showed no significant change in systolic blood pressure.

Conclusion

The above results clearly demonstrate the efficacy of growth hormone treatment in reducing systolic blood pressure in hypertensive animals whose hypertension is either caused by fetal programming or by an adverse postnatal environmental effect such as hypercaloric or hypocaloric nutrition. The very surprising finding of this example is that growth hormone did not reduce blood pressure in the normal control animals.

There are no examples in the literature where growth hormone has caused such a profound fall in systolic blood pressure in a hypertensive animal. Therefore the mechanisms of this effect either by effects on peripheral resistance of by direct action on the heart are unknown. The almost complete normalization of systolic blood pressure in these hypertensive animals is also a surprise.

INDUSTRIAL APPLICATION

Hypertension is a multi-faceted health problem of aging, genetics and, particularly, lifestyle. For example, the combination of post-natal diet and undernutrition causes health problems in terms of high blood pressure. However, the combination of undernutrition or another fetal insult plus cigarette smoking also causes hypertension. Therefore the "programming" plus a post-natal insult (such as hypercaloric or hypocaloric diet) will cause hypertension.

It is believed that the method of the present invention will be effective in treating hypertension, particularly in offspring following fetal intrauterine undernutrition or

growth retardation during pregnancy. The possibility of effective hormonal therapy for the hypertensive population is of immense public health significance.

Although the invention has been described with reference to a particular embodiment, it will be appreciated by those persons skilled in the art that variations and modifications may be made without departing from the spirit and scope of the invention.

CLAIMS

1. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

2. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of administering to the mammal an effective amount of an agent selected from the group consisting of growth hormone, an analog thereof, and a functionally equivalent ligand.

3. A method as claimed in either claim 1 or claim 2 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

4. A method as claimed in any one of claims 1 to 3 wherein the mammal is an adult mammal.

5. A method as claimed claim 4 wherein the mammal is an adult human.

6. A method as claimed in claim 5 wherein the agent administered to the mammal is growth hormone.

7. A method as claimed in any one of the preceding claims wherein the agent is administered to the mammal in combination with a second anti-hypertensive agent.

8. A method of treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

9. A method as claimed in claim 8 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

10. A method as claimed in either claim 8 or claim 9 wherein the effective concentration of the growth hormone, an analog thereof or a functionally equivalent ligand is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

11. A method as claimed in either claim 8 or claim 9 wherein the effective concentration of growth hormone is increased through direct administration of growth hormone.

12. A method as claimed in any one of claims 8 to 11 wherein the mammal is an adult human.

13. The use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, of an agent selected from the group consisting of growth hormone, an analog thereof and a functionally equivalent ligand.

14. The use as claimed in claim 13 wherein the mammal has experienced an adverse postnatal environment comprising a hypocaloric or hypercaloric diet.

15. The use as claimed in either claim 13 or claim 14 wherein the medicament is for treating an adult human.

16. The use as claimed in any one of claims 13 to 15 wherein the agent is growth hormone.

17. The use as claimed in any one of claims 13 to 16 wherein the medicament is for administration in combination with a second anti-hypertensive agent.

18. The use, in the preparation of a medicament for treating hypertension in a mammal, which has experienced intrauterine under nutrition and/or growth retardation or an adverse post-natal environment, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

19. The use as claimed in claim 18 wherein the mammal is an adult human.

Figure 1

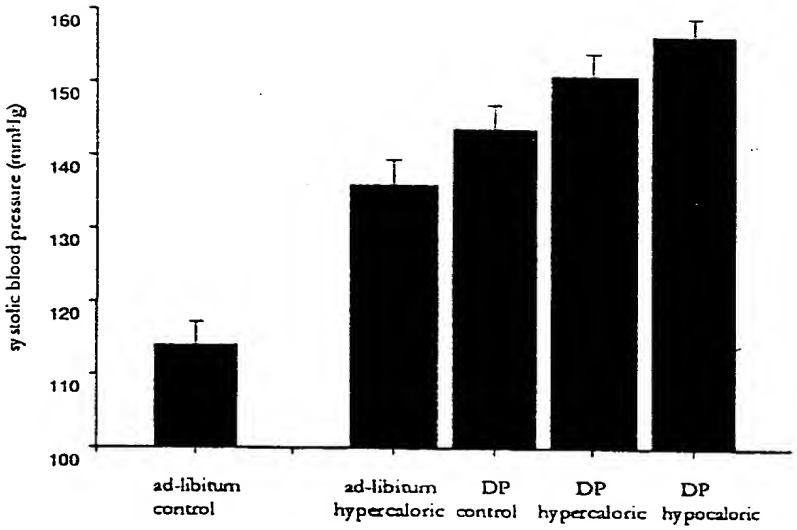
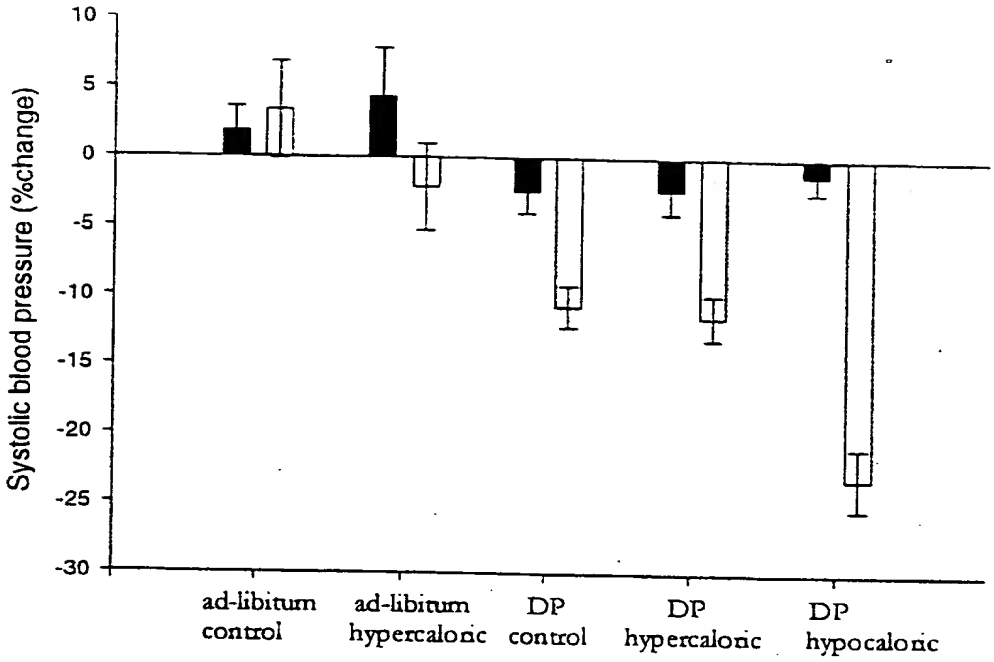

systolic blood pressure (mmHg)
160
150
140
130
120
110
100
ad-libitum control
ad-libitum hypercaloric
DP control
DP hypercaloric
DP hypocaloric

Figure 2


Systolic blood pressure (%change)
10
5
0
-5
-10
-15
-20
-25
-30
ad-libitum control
ad-libitum hypercaloric
DP control
DP hypercaloric
DP hypocaloric

pressure. It is a major risk factor for atherosclerosis. Treatment of high blood pressure can prolong life. Screening programmes reveal that 25% of the general population are hypertensive (Schoen, F.J. (1994). Blood Vessels. In Robbins Pathologic Basis of Disease. Edited by R.S. Cotran, V. Kumar, and F.J. Schoen. Philadelphia: W.B. Saunders Company. 467-516). The prevalence of high blood pressure increases with age. However, in older age groups the disease is usually relatively mild compared to that in young adults where it is often more severe. Approximately 90 to 95% of hypertension is idiopathic and of the remaining 5 to 10%, most is secondary to renal disease. Both primary and secondary hypertension may be either benign or malignant.

In the majority of cases, hypertension remains at a modest level and fairly stable from years to decades. However, if the raised blood pressure is not controlled by anti-hypertensive agents, it frequently causes disability and death from heart failure, and substantially increases the risk of myocardial infarction and strokes. Approximately 5% of people have malignant hypertension where blood pressure rapidly increases and if left untreated, leads to death in one to two years.

Recognising the significance of the problem, it is an object of the present invention to provide a method of treating hypertension, in at least a subset of the population (individuals which experienced intrauterine undernutrition or growth retardation or an adverse postnatal environment), or at least to offer the public a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect the present invention provides a method of treating hypertension in a mammal, the method comprising the step of administering to the mammal an effective amount of an agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

In another aspect, the present invention provides a method of treating hypertension in a mammal, the method comprising the step of administering to the mammal an effective amount of growth hormone, an analog thereof, or a functionally equivalent ligand.

Generally, the hypertensive state of the mammal will be the result of intrauterine fetal programming, or of an unfavorable/adverse postnatal environment (eg. a hypercaloric diet). However, any mammal with hypertension can be treated in accordance with the above methods.

Preferably, the mammal to be treated is an adult mammal.

As used herein, the term "intrauterine undernutrition or growth retardation" means disordered fetal growth with causes which include maternal undernutrition, placental insufficiency, endocrine abnormalities and substance abuse, as evidenced by a relatively low birth weight.

As used herein, "analog" means a protein which is a variant of growth hormone through insertion, deletion or substitution of one or more amino acids but which retains at least substantial functional equivalency.

The term "functionally equivalent ligand" means an agent which binds to and activates the receptors which growth hormone binds to and activates to give the anti-hypertensive effect.

In a further aspect, the invention provides a method of treating hypertension in a mammal, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

The method is particularly suitable for treating a mammal which has experienced either an adverse fetal environment, an adverse postnatal environment, or both.

Preferably, the effective concentration of said growth hormone analog or ligand is increased through direct administration.

Preferably, the effective concentration of growth hormone is increased through direct administration of growth hormone.

Alternatively, the effective concentration of growth hormone is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Preferably, the mammal is an adult human.

In a further aspect, the present invention provides the use of an agent selected from growth hormone, an analog thereof or a functionally equivalent ligand in the preparation of a medicament for treating hypertension in a mammal, such as a mammal which has experienced fetal intrauterine undernutrition or growth retardation.

In yet a further aspect, the invention provides the use, in the preparation of a medicament for treating hypertension in a mammal, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

Preferably, the medicament is for treating hypertension in a mammal which has experienced either an adverse fetal environment, an adverse postnatal environment, or both.

Although the invention is broadly as defined above, it also includes embodiments of which the following description provides examples.

BRIEF DESCRIPTION OF THE DRAWINGS

In particular, the invention will be better understood with reference to the accompanying drawings, in which:

Figure 1 shows the mean systolic blood pressure in *ad-libitum* and developmentally programmed (DP) rat offspring. The data is mean ±SEM with a minimum of 5 animals per group; and

CLAIMS

1. A method of treating hypertension in a mammal, the method comprising the step of administering to the mammal an effective amount of an agent, wherein the agent is a ligand which binds to, and activates, the growth hormone receptor.

2. A method of treating hypertension in a mammal, the method comprising the step of administering to the mammal an effective amount of an agent selected from the group consisting of growth hormone, an analog thereof, and a functionally equivalent ligand.

3. A method as claimed in claim 1 or 2 wherein the mammal has experienced intrauterine undernutrition or growth retardation.

4. A method as claimed in any one of claims 1 to 3 wherein the mammal has experienced an adverse postnatal environment.

5. A method as claimed in claim 4 wherein the adverse postnatal environment comprised a hypocaloric or hypercaloric diet.

6. A method as claimed in any one of claims 1 to 5 wherein the mammal is an adult mammal.

7. A method as claimed in any one of claims 1 to 6 wherein the mammal is an adult human.

8. A method as claimed in claim 7 wherein the agent administered to the mammal is growth hormone.

9. A method as claimed in any one of the preceding claims wherein the agent is administered to the mammal in combination with a second anti-hypertensive agent.

10. A method of treating hypertension in a mammal, the method comprising the step of increasing the effective concentration of growth hormone, an analog thereof or a functionally equivalent ligand in the mammal.

11. A method as claimed in claim 10, wherein the mammal has experienced intrauterine undernutrition or growth retardation.

12. A method as claimed in claim 10 or 11, wherein the mammal has experienced an adverse postnatal environment.

13. A method as claimed in claim 12 wherein the adverse postnatal environment comprised a hypocaloric or hypercaloric diet.

14. A method as claimed in any one of claims 10 to 13, wherein the effective concentration of the growth hormone, an analog thereof or a functionally equivalent ligand is increased through administration of an agent which either stimulates production of growth hormone or which lessens or prevent inhibition of growth hormone activity.

15. A method as claimed in any one of claims 10 to 13, wherein the effective concentration of growth hormone is increased through direct administration of growth hormone.

16. A method as claimed in any one of claims 10 to 15, wherein the mammal is an adult human.

17. The use, in the preparation of a medicament for treating hypertension in a mammal, of an agent selected from the group consisting of growth hormone, an analog thereof and a functionally equivalent ligand.

18. The use as claimed in claim 17 wherein the medicament is for treating a mammal which has experienced intrauterine undernutrition or growth retardation.

19. The use as claimed in claim 17 or 18 wherein the medicament is for treating a mammal which has experienced an adverse postnatal environment.

20. The use as claimed in claim 19 wherein the adverse postnatal environment comprised a hypocaloric or hypercaloric diet.

21. The use as claimed in any one of claims 17 to 20 wherein the medicament is for treating an adult human.

22. The use as claimed in any one of claims 17 to 21 wherein the agent is growth hormone.

23. The use as claimed in any one of claims 17 to 22 wherein the medicament is for administration in combination with a second anti-hypertensive agent.

24. The use, in the preparation of a medicament for treating hypertension in a mammal, of an agent which either stimulates production of growth hormone or which lessens or prevents inhibition of growth hormone activity.

25. The use as claimed in claim 24, wherein the medicament is for treating a mammal which has experienced intrauterine undernutrition or growth retardation.

26. The use as claimed in claim 24 or 25, wherein the mammal has experienced an adverse postnatal environment.

27. The use as claimed in any one of claims 24 to 26, wherein the mammal is an adult human.